



Europäisches Patentamt

European Patent Office

Office européen des brevets

(11) Publication number:

0 177 764

A1

Doc. Ref. FP1  
Appl. No. 10/734,625

## (12) EUROPEAN PATENT APPLICATION

(21) Application number: 85111243.3

(51) Int. Cl.: C 07 D 215/60, C 07 D 405/12,  
A 61 K 31/47

(22) Date of filing: 05.09.85

(30) Priority: 07.09.84 JP 187752/84

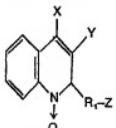
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(34) Designated Contracting States: DE FR GB IT

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## (52) Quinoline-n-oxide derivative and pharmaceutical composition.

(57) A quinoline-N-oxide derivative represented by the formula:



stituted aryl),  $-\text{CH}_2\text{N}^+\text{R}_2\text{R}_3\text{R}_4$ , (wherein R<sub>2</sub>, R<sub>3</sub>, and R<sub>4</sub> are lower alkyl, unsubstituted or substituted aralkyloxy, or unsubstituted or substituted aralkylene, having 3 to 15 carbon atoms; R<sub>1</sub> is alkylene or alkylene, having 3 to 15 carbon atoms; Z is hydroxymethyl, lower alkoxy methyl, unsubstituted or substituted aryloxymethyl, tetrahydrofuranoxymethyl, unsubstituted or substituted arylsulfonyloxymethyl, lower alkylthiomethyl, unsubstituted or substituted arylthiomethyl, lower alkylsulfonylmethyl, lower alkylsulfonylmethyl, lower alkylsulfonimethyl, unsubstituted or substituted arylsulfonimethyl, aminomethyl,  $-\text{CH}_2\text{NH}\text{R}_5$  (wherein R<sub>5</sub> is lower alkyl, unsubstituted or substituted aralkyl, or unsubstituted or substituted aryl),  $-\text{CH}_2\text{NR}_6\text{R}_7$  (wherein R<sub>6</sub> and R<sub>7</sub> are lower alkyl, unsubstituted or substituted aralkyl, or unsubstituted or substituted aryl).

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[wherein X is hydroxy, lower alkoxy, lower alkylthio, unsubstituted or substituted aralkyloxy, or unsubstituted or substituted aralkylene, having 3 to 15 carbon atoms; R<sub>1</sub> is alkylene or alkylene, having 3 to 15 carbon atoms; Z is hydroxymethyl, lower alkoxy methyl, unsubstituted or substituted aryloxymethyl, tetrahydrofuranoxymethyl, unsubstituted or substituted arylsulfonyloxymethyl, lower alkylthiomethyl, unsubstituted or substituted arylthiomethyl, lower alkylsulfonylmethyl, lower alkylsulfonimethyl, unsubstituted or substituted arylsulfonimethyl, aminomethyl,  $-\text{CH}_2\text{NH}\text{R}_5$  (wherein R<sub>5</sub> is lower alkyl, unsubstituted or substituted aralkyl, or unsubstituted or substituted aryl),  $-\text{CH}_2\text{NR}_6\text{R}_7$  (wherein R<sub>6</sub> and R<sub>7</sub> are lower alkyl, unsubstituted or substituted aralkyl, or unsubstituted or substituted aryl).

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DR.-ING. JÜRGEN SCHMIDT-BOGATZKY\*QUINOLINE-N-OXIDE DERIVATIVE AND  
PHARMACEUTICAL COMPOSITIONEDUARD-SCHMID-STRASSE 2  
8000 MÜNCHEN 90

Priority: Sept. 7, 1984-Japan-No. 187752/84

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P 2644-EPBackground of the Invention

The present invention relates to a quinoline-N-oxide derivative having a lipoxygenase-inhibiting action

10 and a pharmaceutical composition containing the same.

Lipoxygenase (1. 13. 11. 12) is an enzyme existing in blood platelets, leukocytes, lymphocytes, etc., and converts polyvalent unsaturated fatty acid (particularly arachidonic acid) to hydroperoxy acid. It is known that positions of hydroperoxy group(s) introduced in arachidonic acid by lipoxygenase are 5th, 8th, 9th, 11th, 12th and 15th positions. For example, it has been reported that lipoxygenase existing mostly in blood platelets, etc. is an enzyme that hydroperoxidizes the 12th position of

20 arachidonic acid (12-lipoxygenase), and there are 5-lipoxygenase and 15-lipoxygenase in leukocytes. Hydroperoxyeicosatetraenoic acid formed from arachidonic acid by lipoxygenase is unstable and is converted to hydroxyeicosatetraenoic acid. These fatty acids formed by

25 lipoxygenase stimulate by themselves physiological actions such as migration of leukocytes and smooth muscles of aortic tunica media, etc., and it has been recently clarified that they are further metabolized in vivo to produce metabolic products having various physiological

30 actions. For example, chemical structure and biosynthesis route of a slow reacting substance of anaphylaxis (abbreviated as SRS-A, which includes leukotriene C, D, E and F) which is formed in lungs of guinea pigs at anaphylaxis or human lungs at asthmatic attacks and has a force to slowly but strongly contract the smooth muscles of bronchus and which has long been regarded as a substance to cause asthma have been recently clarified by Samuelson et al.

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[Proc. Natl. Acad. Sci. U.S., 77, 2014 (1980)], and it has been found that it is formed by metabolism from arachidonic acid by aid of 5-lipoxygenase. It has been reported that various peroxy lipids such as hydroperoxyeicosatetraenoic acid, hydroxyeicosatetraenoic acid, leucotriene B, SRS-A, etc. which are formed by metabolism by aid of lipoxygenase, are chemical mediators that contract various smooth muscles, for example, smooth muscles of respiratory system (trachea, bronchus, pulmonary tissue), vascular system, digestive organ; accelerate capillary permeability, stimulate migration of leukocytes and smooth muscles of aortic tunica media, and as the result cause bronchial asthma, allergic diseases (atopic dermatitis, inflammation of organs, etc.), diseases of circulatory organs (edema, ischemic heart disease, hypertension, ischemic brain disturbance, arteriosclerosis, etc.) or cause inflammatory diseases.

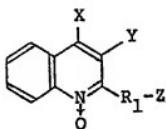
However, studies of effective compounds on the diseases caused by the lipoxygenase metabolites have not been advanced yet.

As a result of searching preventive and healing agents for the diseases caused by the lipoxygenase metabolites, it has been found that quinoline-N-oxide derivatives are useful as preventive and healing agents, for the diseases caused by the lipoxygenase metabolites.

#### Summary of the Invention

The present invention relates to a quinoline-N-oxide derivative represented by the formula (I):

30



(I)

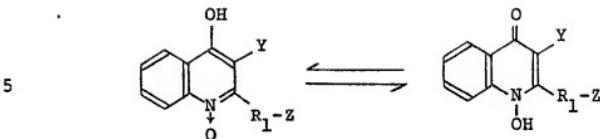
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[wherein X is hydroxy, lower alkoxy, lower alkylthio, unsubstituted or substituted aralkyloxy, or unsubstituted

or substituted aralkylthio; Y is a hydrogen atom or halogen atom; R<sub>1</sub> is alkylene or alkenylene having 3 to 15 carbon atoms; Z is hydroxymethyl, lower alkoxymethyl, unsubstituted or substituted aryloxymethyl, tetrahydro-  
5 pyranyloxymethyl, tetrahydrofuranyloxymethyl, unsubstituted or substituted arylsulfonyloxymethyl, lower alkylthiomethyl, unsubstituted or substituted arylthiomethyl, lower alkylsulfinylmethyl, unsubstituted or substituted arylsulfinylmethyl, lower alkylsulfonylmethyl, unsubstituted  
10 or substituted arylsulfonylmethyl, aminomethyl, -CH<sub>2</sub>NHR<sub>2</sub> (wherein R<sub>2</sub> is lower alkyl, unsubstituted or substituted aralkyl, or unsubstituted or substituted aryl), -CH<sub>2</sub>NR<sub>3</sub>R<sub>4</sub> (wherein R<sub>3</sub> and R<sub>4</sub> are lower alkyl, unsubstituted or substituted aralkyl, or unsubstituted or substituted aryl),  
15 -CH<sub>2</sub>N<sup>+</sup>R<sub>5</sub>R<sub>6</sub>R<sub>7</sub> (wherein R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are lower alkyl, unsubstituted or substituted aralkyl, or unsubstituted or substituted aryl, where the counterion is an anion of acid or a hydroxyl ion), -COR<sub>8</sub> (wherein R<sub>8</sub> is a hydrogen atom, lower alkyl or hydroxy, -CH(OR<sub>9</sub>)<sub>2</sub> (wherein R<sub>9</sub> is lower alkyl), iminomethyl, hydroxyiminomethyl or a halogen atom) [hereinafter referred to as "compound (I)", and compounds of other formula numbers will be hereinafter likewise referred to] and its salts, and a pharmaceutical composition containing a compound (I) or a pharmacologically acceptable salt thereof. Compounds (I) and their salts can very strongly inhibit the lipoxygenase and considerably suppress production and release of its metabolites, and thus are useful as preventive and healing agents for the diseases caused by the lipoxygenase metabolites.  
20  
25  
30

Detailed Description of the Invention

The compound (I) where X=OH can exist as a tautomer as shown by the following equation, and thus it is needless to say that the present invention includes these tautomers:  
35



10

In the definitions of the respective groups in the formula (I), the lower alkyl appearing in the lower alkoxy, lower alkylthio, lower alkylsulfinyl, lower alkylsulfonyl, and lower alkyl includes linear or branched alkyls having 1 to 4 carbon atoms, for example, methyl, ethyl, n-propyl, i-propyl, n-butyl, etc.

In the definitions of the respective groups, the aralkyl appearing in the aralkyloxy, aralkylthio, and aralkyl includes those whose aryl moiety is phenyl or naphthyl and whose alkyl moiety is alkyl having 1 to 3 carbon atoms, for example, methyl, ethyl, etc.

In the definitions of the respective groups, the aryl appearing in the aryloxy, arylthio, arylsulfonyl, and aryl is phenyl or naphthyl. The substituent appearing in the substituted aralkyloxy, substituted aralkylthio, substituted aralkyl, substituted aryloxymethyl, substituted arylsulfonyloxy, substituted arylthiomethyl, substituted arylsulfinylmethyl, substituted arylsulfonylmethyl, and substituted aryl is a substituent on the aryl ring and includes lower alkyl, lower alkoxy, halogen atoms (chlorine, bromine, etc.), nitro, hydroxyl, etc., where the lower alkyl and lower alkoxy have the same meanings as defined above.

In the definitions of the respective groups in the formula (I), the halogen atom includes chlorine, bromine, iodine, etc. The alkylene and alkenylene having 3 to 15 carbon atoms as  $R_1$  are linear or branched, and

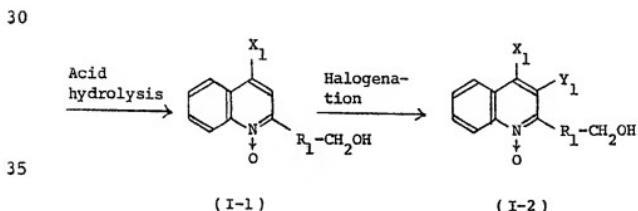
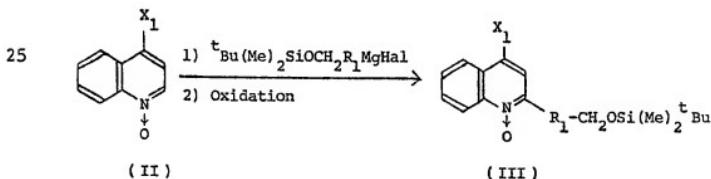
include, for example, trimethylene, pentamethylene, heptamethylene, octamethylene, nonamethylene, decamethylene, undecamethylene, dodecamethylene, tridecamethylene, tetradecamethylene, pentadecamethylene, propenylene, etc.

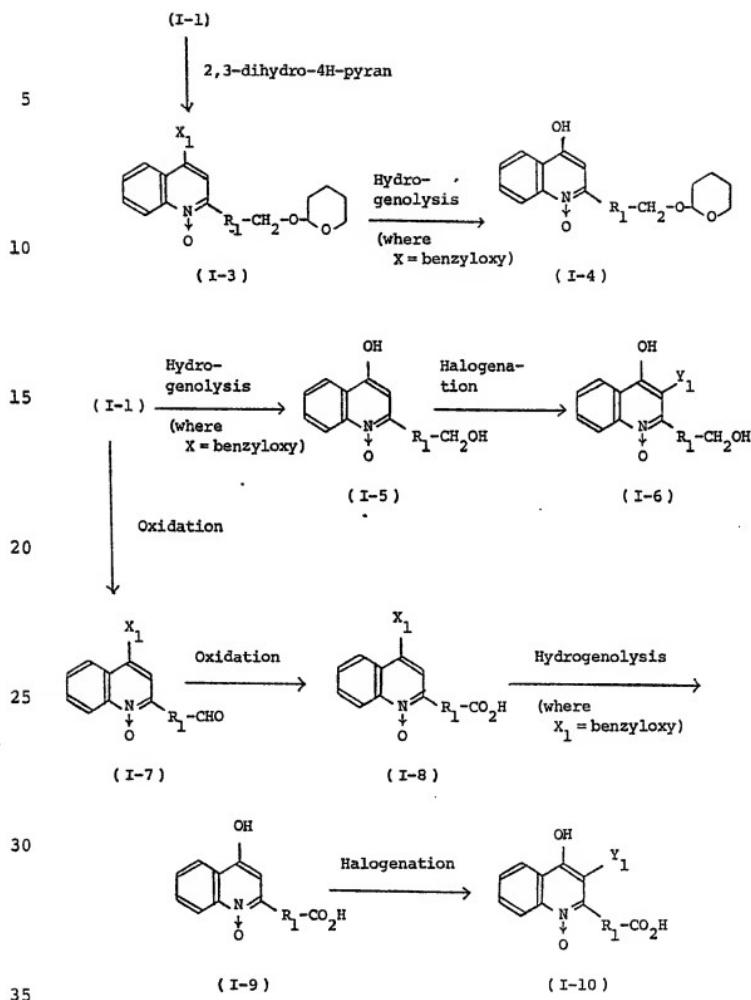
5 From the viewpoint of pharmacological effect, alkylene and alkenylene having 5 to 15 carbon atoms are preferable.

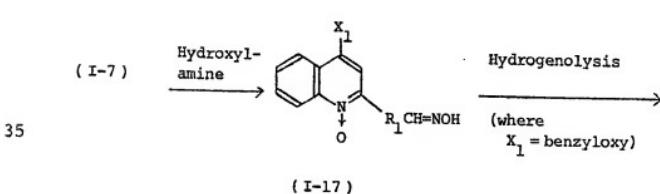
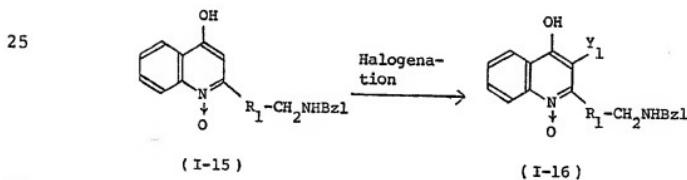
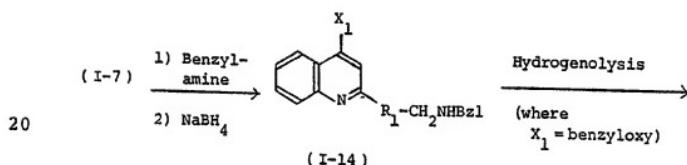
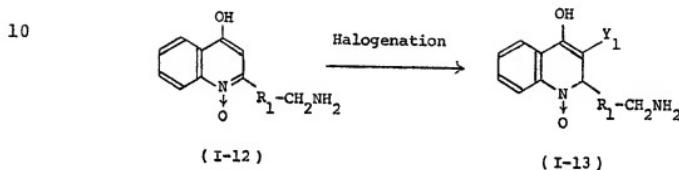
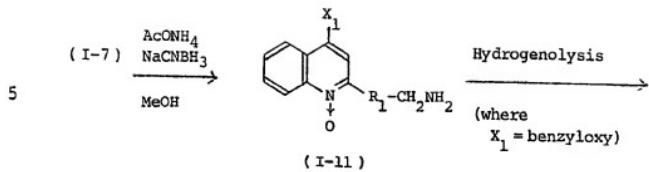
When the compound (I) is an acidic compound, a base addition salt can be prepared, whereas when it is a basic compound, an acid addition salt can be prepared.

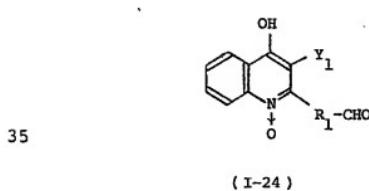
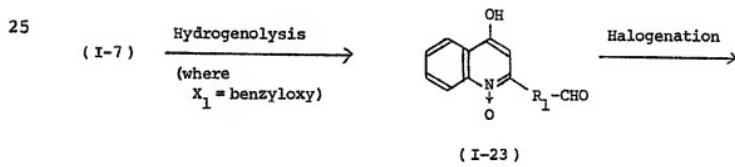
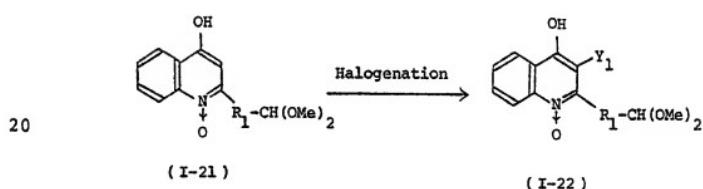
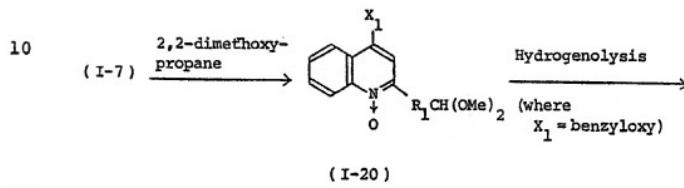
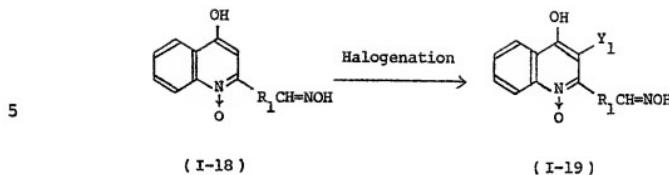
10 The salt of the acidic compound is preferably a pharmaco-  
logically acceptable salt, and includes alkali metal  
salts such as sodium salt and potassium salt, alkaline  
earth metal salts such as calcium salt and magnesium salt,  
and salts of organic bases such as ethanalamine, triethyl-  
15 amine, morpholine, piperidine, piperazine, etc. The acid  
salt of the basic compound includes inorganic and organic  
acid salts, and such an acid salt is preferably a pharmaco-  
logically acceptable salt and includes, for example,  
hydrochloride, sulfate, nitrate, acetate, oxalate,  
20 fumarate, citrate, etc.

The compound (I) can be prepared according to the following reaction procedures:









(wherein  $X_1$  is X excluding hydroxy, that is, lower alkoxy, lower alkylthio, unsubstituted or substituted aralkyloxy, or unsubstituted or substituted aralkylthio;  $Y_1$  is Y excluding hydrogen, that is, a halogen atom;  $R_1$  has the same meaning as defined above; Hal is a halogen atom, for example, chlorine, bromine, and iodine).

First of all, compound (III) is prepared by reaction of compound (II) with a Grignard's reagent [prepared from  $t\text{-Bu}(\text{Me})_2\text{SiOCH}_2\text{R}_1\text{Hal}$  and magnesium].

The reaction can be carried out in an ethereal solvent such as tetrahydrofuran, dioxane, etc. under mild conditions nearly at room temperature or below. It is preferable to use at least about one mole, preferably about 1.5 to about 2 moles of the Grignard's reagent per mole of the compound (II). After the reaction, the remaining excess Grignard's reagent is decomposed, for example, by adding water thereto, and then the solvent is removed therefrom by distillation. The residues thus obtained are dissolved in an appropriate inert solvent, for example, a halogenated hydrocarbon such as methylene chloride, chloroform, carbon tetrachloride, etc., and the solution is treated with an organic peroxide, for example, perbenzoic acid, m-chloroperbenzoic acid, peracetic acid, etc. in a substantially equimolar amount or a little excess amount, in respect to the compound (II), with ice cooling, whereby the compound (III) can be obtained.

The compound (III) thus obtained is subjected to hydrolysis reaction with hydrochloric acid, etc. in a solvent, for example, alcohol such as methanol, ethanol, propanol, etc., acetone, etc. at room temperature, whereby compound (I-1) can be obtained.

Then, the compound (I-1) is halogenated, if necessary, whereby compound (I-2) can be obtained. The halogenation can be carried out according to the ordinary procedure using the ordinary halogenating agent, such as N-chlorosuccinimide, N-bromosuccinimide, etc. For example, when the halogenation is carried out with N-halosuccinimide,

the compound (I-1) is dissolved in an appropriate solvent, for example, an alcohol such as methanol, ethanol, etc., or a halogenated hydrocarbon such as dichloromethane, chloroform, etc., and a substantially equimolar amount of  
5 N-halosuccinimide is added thereto. Then, the mixture is stirred at room temperature, whereby the compound (I-1) can be converted to the compound (I-2).

On the other hand, the compound (I-1) is dissolved in an appropriate inert solvent, for example, a  
10 halogenated hydrocarbon such as methylene chloride, chloroform, carbon tetrachloride, etc., and treated with dihydro-  
pyran in a substantially equimolar amount or a little excess amount in respect to the compound (I-1) and a catalytic amount of p-toluenesulfonic acid or a catalytic  
15 amount of D-camphorsulfonic acid or the like at room temperature, whereby the compound (I-1) can be converted to compound (I-3). A compound (I-3) wherein  $X_1$  is a benzyloxy group can be converted to compound (I-4) by a well-known hydrogenolysis reaction. For example, the  
20 compound (I-4) can be obtained by reducing the compound (I-3) with hydrogen under the atmospheric pressure or under a superatmospheric pressure at room temperature in a solvent such as methanol, ethanol, etc. in the presence of a hydrogenating catalyst such as palladium-carbon,  
25 platinum black, Raney nickel, etc. On the other hand, compound (I-5) can be obtained by hydrogenolyzing a compound (I-1) where  $X_1$  is a benzyloxy group in the same manner as described above. Compound (I-6) can be obtained, if necessary, by halogenating the compound (I-5) in the  
30 same manner as described above. The compound (I-1) can be converted to compound (I-7) by dissolving the compound (I-1) in an appropriate inert solvent, for example, a halogenated hydrocarbon such as methylene chloride, chloroform, carbon tetrachloride, etc. and oxidizing the compound  
35 (I-1) with pyridinium chlorochromate in a substantially equimolar amount or an excess amount in respect to the compound (I-1) at room temperature.

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Furthermore, the compound (I-7) can be converted to compound (I-8) by dissolving the compound (I-7) in a solvent such as acetone, etc., and treating the compound (I-7) with an excess amount of Jones' reagent with ice cooling. A compound (I-8) where  $X_1$  is a benzyloxy group can be converted to compound (I-9) by hydrogenolysis in the same manner as above, and furthermore the compound (I-9) can be converted to compound (I-10), if necessary, by halogenation in the same manner as above.

On the other hand, the compound (I-7) can be converted to compound (I-11) by treating the compound (I-7) with ammonium acetate and sodium cyanoborohydride in a solvent such as methanol, ethanol, etc. with ice cooling. A compound (I-11) where  $X_1$  is a benzyloxy group can be converted to compound (I-12) by hydrogenolysis in the same manner as above, and furthermore the compound (I-12) can be converted to compound (I-13), if necessary, by halogenation in the same manner as above.

The compound (I-7) can be converted to compound (I-14) by treatment with benzylamine in a solvent such as methanol, ethanol, etc. at room temperature and then by reduction with sodium borohydride with ice cooling. A compound (I-14) where  $X_1$  is a benzyloxy group can be converted to compound (I-15) by hydrogenolysis in the same manner as above, and furthermore the compound (I-15) can be converted to compound (I-16), if necessary, by halogenation in the same manner as above.

Furthermore, the compound (I-7) can be converted to compound (I-17) by treatment with hydroxylamine hydrochloride at room temperature in a solvent such as methanol, ethanol, etc. A compound (I-17) where  $X_1$  is a benzyloxy group can be converted to compound (I-18) by hydrogenolysis in the same manner as above, and furthermore the compound (I-18) can be converted to compound (I-19), if necessary, by halogenation in the same manner as above.

Furthermore, the compound (I-7) can be converted to compound (I-20) by adding compound (I-7) and 2,2-

dimethoxypropane to an appropriate inert solvent such as methylene chloride, chloroform, carbon tetrachloride, etc. and stirring the mixture in the presence of an acid catalyst such as p-toluenesulfonic acid, D-camphorsulfonic acid, etc. at room temperature. A compound (I-20) where X<sub>1</sub> is a benzyloxy group can be converted to compound (I-21) by hydrogenolysis in the same manner as above, and the compound (I-21) can be converted to compound (I-22) by halogenation in the same manner as above.

10 Furthermore, a compound (I-7) where X<sub>1</sub> is a benzyloxy group can be converted to compound (I-23) by hydrogenolysis in the same manner as above, and the compound (I-23) can be converted to compound (I-24), if necessary, by halogenation in the same manner as above.

15 The compound (I) thus prepared, i.e. compounds (I-1) to (I-24) can be purified by a well-known purification procedure, for example, by recrystallization, column chromatography using silica gel, etc., extraction, etc.

The present invention also relates to a preventive 20 and healing composition for diseases due to lipoxygenase metabolic products, which comprises an effective amount of a compound (I) or a pharmacologically acceptable salt thereof, and at least one pharmaceutically acceptable carrier. The compound (I) and its salts strongly inhibit

25 the lipoxygenase activity. The compound (I) and its pharmacologically acceptable salts are useful for healing and preventing, or treating bronchial asthma, various allergic diseases (allergic rhinitis, urticaria, etc.), ischemic heart disease, hypertension, ischemic brain disturbance, 30 arteriosclerosis, inflammatory diseases, etc., caused by lipoxygenase metabolites. Dosage for these purposes depends upon the desired healing effect, way of administration, healing period, age, body weight, etc., and usually is 0.5 - 20 mg/kg per day for an adult human as compounds 35 (I) through oral or parenteral route (for example, injection, application, inhalation, etc.). Compound (I) or a salt thereof can be administered as such, but generally

administered in the form of tablets, pills, powder,  
granules, capsules, suppository, injection, etc. Carriers  
used for the pharmaceutical composition include lactose,  
dextrose, sucrose, sorbitol, mannitol, glucose, cellulose,  
5 cyclodextrin, talc, starch, methylcellulose, gelatin,  
arabic gum, polyethylene glycol, carboxymethylcellulose,  
hydroxypropylcellulose, sodium benzoate, sodium hydrogen  
sulfite, aluminium stearate, magnesium stearate, mineral  
oil, vegetable oil, white vaseline, liquid paraffin, etc.,  
10 and can be appropriately selected in view of the kind of  
preparations. The present composition can contain 0.01-  
85 weight percent of compound (I).

Examples and Experimental Example of the present  
invention are given below:

15

Example 1

1-(1) Preparation of 4-benzyloxy-2-(11-t-butyl-  
dimethylsilyloxyundecyl) quinoline-N-oxide

20 The Grignard's reagent prepared from 7.5 m moles  
of 11-t-butyldimethylsilyloxyundecyl bromide and 7.5 m moles  
of magnesium is dropwise added to a tetrahydrofuran solu-  
tion containing 5 m moles of 4-benzyloxyquinoline-N-oxide  
with ice cooling and the mixture is stirred at the same  
25 temperature for one hour. Then, water is added by portions  
thereto to decompose the reagent, and then the mixture is  
extracted with chloroform. The solvent is removed from  
the extract by distillation, and the residue is dissolved  
in methylene chloride, and an aqueous saturated solution  
30 of sodium hydrogen carbonate is added to the solution, and  
further 5 m moles of ice-cooled metachloroperbenzoic acid  
is added thereto. Then, the mixture is stirred for 30  
minutes. Then, the reaction solution is washed with an  
aqueous saturated solution of sodium hydrogen carbonate  
35 and then with water, and dried over anhydrous sodium  
sulfate. Then, the solvent is removed therefrom by dis-  
tillation. The residue is purified by silica gel column

procedure, whereby the captioned compound can be obtained as a colorless oily substance (yield: 88.0%).

NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm): 0.35(6H, s, Me x 2), 0.86(9H, s, Me x 3), 3.14(2H, t, J=6Hz,  $\text{ArCH}_2$ ), 3.61(2H, t, J=6Hz,  $-\text{OCH}_2$ ), 5.30(2H, s,  $\text{OCH}_2\text{Ar}$ ), 6.70(1H, s, ArH), 8.28(1H, dd, J=1.5Hz, 8Hz, ArH), 8.87(1H, dd, J=1.5Hz, 8Hz, ArH)

1-(2) Preparation of 4-benzyloxy-2-(11-hydroxy-  
undecyl) quinoline-N-oxide

At first, 5 m moles of 4-benzyloxy-2-(11-t-butyl-dimethylsilyloxyundecyl) quinoline-N-oxide is dissolved in methanol, and an aqueous 10% hydrochloric acid solution is added thereto. Then, the mixture is stirred at room temperature for 3 hours. After removal of the solvent therefrom by distillation, the residue is extracted with chloroform, and the extract is washed with an aqueous saturated sodium hydrogen carbonate solution, and then with water, and dried over anhydrous sodium sulfate, and the solvent is removed therefrom by distillation. The residue is purified by silica gel column procedure, whereby the captioned compound is obtained as colorless crystals (yield: 88.4%).

NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm): 3.12(2H, t, J=7.5Hz,  $\text{ArCH}_2$ ), 3.60(2H, t, J=6Hz,  $\text{CH}_2\text{OH}$ ), 5.30(2H, s,  $\text{OCH}_2\text{Ar}$ ), 6.69(1H, s, ArH), 8.25(1H, dd, J=1.5Hz, 8Hz, ArH), 8.79(1H, dd, J=1.5Hz, 8.5Hz, ArH)

Example 2

In the same manner as in Example 1, 4-benzyloxy-2-(3-hydroxypropyl) quinoline-N-oxide is obtained.

NMR ( $\text{CDCl}_3 + \text{CD}_3\text{OD}$ )  $\delta$  (ppm): 2.40(2H, q, J=5Hz,  $\text{CH}_2-\text{CH}_2\text{CH}_2$ ), 3.29(2H, t, J=5Hz, Ar- $\text{CH}_2-$ ), 3.68(2H, t, J=5Hz,  $\text{CH}_2\text{OH}$ ), 5.40(2H, s,  $-\text{OCH}_2\text{Ar}$ ), 6.98(1H, s, ArH), 8.38(1H, dd, J=1.5Hz, 8Hz, ArH), 8.74(1H, dd, J=1.5Hz, 8Hz, ArH).

Example 3

Preparation of 4-hydroxy-2-(11-hydroxyundecyl) quinoline-N-oxide

In this example, 4-benzyloxy-2-(11-hydroxyundecyl) quinoline-N-oxide is dissolved in methanol and catalytically reduced with a catalyst of 10% palladium-carbon under the atmospheric pressure. Then, the catalyst is removed therefrom by filtration, and the solvent is also removed therefrom by distillation. The residue is recrystallized from ethanol, whereby the cationed compound is obtained (yield: 57.5%).

NMR ( $\text{CDCl}_3 + \text{CD}_3\text{OD}$ )  $\delta$  (ppm): 2.91(2H, t,  $J=6\text{Hz}$ ,  $\text{CH}_2\text{Ar}$ ),  
3.57(2H, t,  $J=6\text{Hz}$ ,  $\text{CH}_2\text{OH}$ ), 6.35(1H, s,  $\text{ArH}$ ),  
8.16(1H, dd,  $J=1.5\text{Hz}$ , 8Hz,  $\text{ArH}$ ), 8.30(1H, dd,  
15  $J=1.5\text{Hz}$ , 8Hz,  $\text{ArH}$ )

Example 4

In the same manner as in Example 3, 4-hydroxy-2-[3-(2-tetrahydropyranloxy) propyl] quinoline-N-oxide is obtained.

NMR ( $\text{CDCl}_3 + \text{CD}_3\text{OD}$ )  $\delta$  (ppm): 2.34(2H, q,  $J=6\text{Hz}$ ,  
- $\text{CH}_2\text{CH}_2\text{CH}_2-$ ), 2.90(2H, t,  $J=6\text{Hz}$ ,  $\text{ArCH}_2-$ ),  
4.54(1H, br.s, - $\text{O}-\text{CH}_2-\text{O}-$ ), 6.21(1H, s,  $\text{ArH}$ ),  
8.14(1H, dd,  $J=1.5\text{Hz}$ , 8Hz,  $\text{ArH}$ ), 8.29(1H, dd,  
25  $J=1.5\text{Hz}$ , 8Hz,  $\text{ArH}$ ).

Example 5

Preparation of 3-bromo-4-hydroxy-2-(11-hydroxyundecyl) quinoline-N-oxide

In this example, 1 m mole of 4-hydroxy-2-(11-hydroxyundecyl) quinoline-N-oxide is dissolved in a liquid mixture of methanol - chloroform (5 : 1), and 1 m mole of N-bromosuccinimide is added thereto. The mixture is stirred at room temperature for one hour. After the reaction, the solvent is removed therefrom by distillation, and the residue is recrystallized from ethanol, whereby the captioned compound is obtained (yield: 70.5%).

NMR ( $\text{CDCl}_3 + \text{CD}_3\text{OD}$ )  $\delta$  (ppm): 3.25(2H, t, J=6.5Hz,  $\text{ArCH}_2-$ ), 3.91(2H, t, J=6Hz,  $\text{CH}_2\text{OH}$ ), 7.96(1H, dd, J=1.5Hz, 8Hz, ArH), 8.36(1H, dd, J=1.5Hz, 8Hz, ArH).

5

Example 6

Preparation of 4-benzyloxy-2-[11-(2-tetrahydro-pyranloxy) undecyl] quinoline-N-oxide

In this example, 5 m moles of 4-benzyloxy-2-(11-hydroxyundecyl)-quinoline-N-oxide is dissolved in dichloromethane, and a catalytic amount of D-camphorsulfonic acid and 6 m moles of 2,3-dihydropyran are added thereto. The mixture is stirred at room temperature for 3 hours. Then, the reaction solution is washed with an aqueous sodium hydrogen carbonate solution and then with water, and dried over anhydrous sodium sulfate. The solvent is removed therefrom by distillation, and the residue is purified by silica gel column procedure, whereby the cationed compound is obtained as a colorless oily substance (yield: 82.3%).

NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm): 3.13(2H, t, J=6.5Hz,  $\text{CH}_2\text{Ar}$ ), 4.55(1H, t, J=2Hz,  $-\text{OCHO}-$ ), 5.27(2H, s,  $\text{OCH}_2\text{Ar}$ ), 6.68(1H, s, ArH), 8.27(1H, dd, J=1.5Hz, 8Hz, ArH), 8.83(1H, dd, J=1.5Hz, 8Hz, ArH).

25   Example 7

Preparation of 4-benzyloxy-2-(10-formyldecyl) quinoline-N-oxide

In this example, 5 m moles of 4-benzyloxy-2-(11-hydroxyundecyl) quinoline-N-oxide is dissolved in dichloromethane, and 15 m moles of pyridinium chlorochromate is added thereto. Then, the mixture is stirred at room temperature for 2.5 hours. The reaction solution is washed with water and dried over anhydrous sodium sulfate, and the solvent is removed therefrom by distillation. The residue is purified by silica gel column procedure, whereby the captioned compound is obtained as a colorless oily substance (yield: 79.2%).

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NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm): 2.40(2H, t, J=6Hz,  $\text{CH}_2\text{Ar}$ ),  
3.16(2H, t, J=8Hz,  $\text{CH}_2\text{CHO}$ ), 5.31(2H, s,  $\text{OCH}_2\text{Ar}$ ),  
6.70(1H, s,  $\text{ArH}$ ), 8.26(1H, dd, J=1.5Hz, 8Hz,  
ArH), 8.84(1H, dd, J=1.5Hz, 8Hz,  $\text{ArH}$ ), 9.77(1H,  
6, J=2Hz,  $\text{CHO}$ ).

Example 8

Preparation of 4-benzyloxy-2-(10-carboxydecyl) quinoline-N-oxide

In this example, 5 m moles of 4-benzyloxy-2-(10-formyldecyl) quinoline-N-oxide is dissolved in acetone, and 10 m moles of Jones' reagent prepared from chromium trioxide, sulfuric acid and water is added thereto with ice cooling. The mixture is stirred for 5 minutes. After the reaction, water is added thereto, and the reaction mixture is extracted with chloroform. The extract is dried over anhydrous sodium sulfate, and then the solvent is removed therefrom by distillation. The residue is purified by silica gel column procedure, whereby the captioned compound is obtained as colorless crystals (yield: 31.0%).

NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm): 2.32(2H, t, J=6.5Hz,  $\text{CH}_2\text{Ar}$ ),  
3.22(2H, t, J=8.0Hz,  $\text{CH}_2\text{CO}_2\text{H}$ ), 5.33(2H, s,  
 $\text{OCH}_2\text{Ar}$ ), 6.76(1H, s,  $\text{ArH}$ ), 8.32(1H, dd, J=1Hz,  
8Hz,  $\text{ArH}$ ), 8.83(1H, dd, J=1Hz, 8Hz,  $\text{ArH}$ ).

Example 9

Preparation of 4-benzyloxy-2-(11-aminoundecyl) quinoline-N-oxide

In this example, 5 m moles of 4-benzyloxy-2-(10-formyldecyl) quinoline-N-oxide is dissolved in methanol, and 50 m moles of ammonium acetate and 15 m moles of sodium cyanoborohydride are added thereto with ice cooling. Then, the mixture is stirred for 1.5 hours. After the reaction, the solvent is removed therefrom by distillation, and then the mixture is extracted with chloroform. The chloroform layer is dried over anhydrous sodium sulfate, and the

solvent is removed therefrom by distillation. The residue is purified by silica gel column procedure, whereby the captioned compound is obtained as colorless crystals (yield: 21.5%).

5        NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm): 2.60(2H, br.s,  $\text{CH}_2\text{NH}_2$ ), 3.16  
            (2H, t, J=8Hz,  $\text{CH}_2\text{Ar}$ ), 5.30(2H, s,  $\text{OCH}_2\text{Ar}$ ),  
            6.71(1H, s,  $\text{ArH}$ ), 8.30(1H, dd, J=1Hz, 8Hz,  $\text{ArH}$ ),  
            8.85(1H, dd, J=1Hz, 8Hz,  $\text{ArH}$ )

10      Example 10

Preparation of 4-benzyloxy-2-[11-(N-benzylamino-undecyl)] quinoline-N-oxide

In this example, 5 m moles of 4-benzyloxy-2-(10-formyldecyl) quinoline-N-oxide is dissolved in ethanol, 15 and 5 m moles of benzylamine is added thereto. Then, the mixture is stirred at room temperature for two hours. Then, the solvent is removed therefrom by distillation, and an aqueous saturated sodium hydrogen carbonate solution is added to the residue. Then, the mixture is extracted 20 with chloroform. The solvent is removed therefrom by distillation, and the residue is dissolved in methanol, and 10 m moles of sodium borohydride is added thereto. The mixture is stirred with ice cooling for one hour. The solvent is removed therefrom by distillation, and the 25 residue is extracted with chloroform. The chloroform layer is dried over anhydrous sodium sulfate, and then the solvent is removed therefrom by distillation. The residue is purified by silica gel column procedure, whereby the captioned compound is obtained as a colorless oily substance (yield: 65.5%).

30        NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm): 2.62(2H, t, J=6.5Hz,  $\text{NHCH}_2$ )  
            3.15(2H, t, J=8Hz,  $\text{CH}_2\text{Ar}$ ), 3.89(2H, s,  $\text{NHCH}_2\text{Ar}$ ),  
            5.30(2H, s,  $\text{OCH}_2\text{Ar}$ ), 6.68(1H, s,  $\text{ArH}$ ), 8.26  
            (1H, dd, J=1Hz, 8Hz,  $\text{ArH}$ ), 8.86(1H, dd, J=1Hz,  
            8Hz,  $\text{ArH}$ ).

Example 11

Preparation of 4-benzyloxy-2-[10-(N-hydroxy-iminodecyl) quinoline-N-oxide]

In this example, 5 m moles of 4-benzyloxy-2-(10-formyldecyl) quinoline-N-oxide is dissolved in methanol and 5 m moles of hydroxylamine hydrochloride is added thereto. The mixture is stirred at room temperature for 3 hours. The solvent is removed therefrom by distillation, and an aqueous saturated sodium hydrogen carbonate solution is added to the residue. Then, the mixture is extracted with chloroform, and the organic layer is dried over anhydrous sodium sulfate. Then, the solvent is removed therefrom by distillation, and the residue is purified by silica gel column procedure, whereby the captioned compound is obtained as a colorless oily substance (yield: 72.0%).

NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm): 2.15(1H, q,  $J=6\text{Hz}$ ,  $\text{HCH}-\text{CH}=\text{N}-$ ), 2.30(1H, q,  $J=6\text{Hz}$ ,  $\text{HCH}-\text{CH}=\text{N}-$ ), 3.17(2H, t,  $J=8\text{Hz}$ ,  $\text{CH}_2\text{Ar}$ ), 5.31(2H, s,  $\text{OCH}_2\text{Ar}$ ), 6.71(1H, s,  $\text{ArH}$ ), 8.28(1H, dd,  $J=1\text{Hz}$ , 8Hz,  $\text{ArH}$ ), 8.89(1H, dd,  $J=1\text{Hz}$ , 8Hz,  $\text{ArH}$ ).

Example 12

Preparation of 4-benzyloxy-2-(11,11-dimethoxy-undecyl) quinoline-N-oxide

In this example, 5 m moles of 4-benzyloxy-2-(10-formyldecyl) quinoline-N-oxide is dissolved in dichloromethane, and a catalytic amount of D-camphorsulfonic acid and a large excess of 2,2-dimethoxypropane are added thereto. The mixture is stirred at room temperature for 3 hours. After the reaction, the reaction solution is washed with an aqueous saturated sodium hydrogen carbonate solution, and then with water, and dried over anhydrous sodium sulfate. After removal of the solvent by distillation, the residue is purified by silica gel column procedure, whereby the captioned compound is obtained as a colorless oily substance (yield: 70.6%).

NMR ( $\text{CDCl}_3$ )  $\delta$  (ppm): 3.16 (2H, t,  $J=7\text{Hz}$ ,  $\text{CH}_2\text{Ar}$ ),  
 3.36 (6H, s, OMe  $\times 2$ ), 4.38 (1H, t,  $J=5\text{Hz}$ ,  $\text{CH}(\text{OMe})_2$ ),  
 5.32 (2H, s,  $\text{OCH}_2\text{Ar}$ ), 6.71 (1H, s, ArH), 8.30 (1H,  
 dd,  $J=1\text{Hz}$ , 8Hz, ArH), 8.87 (1H, dd,  $J=1\text{Hz}$ , 8Hz,  
 5 ArH).

Examples 13 - 20

In the same manner as in Examples 1 and 3, compounds shown in the following Table 1 are obtained.

10

Table 1

Ex. No.	Compound	NMR $\delta$ (ppm)
15	13 4-benzyloxy-2-[3-(2-tetrahydropyranoyloxy) propyl] quinoline-N-oxide	$\text{CDCl}_3$ , 2.12 (2H, t, $J=7.5\text{Hz}$ , $\text{CH}_2\text{CH}_2\text{CH}_2$ ), 3.23 (2H, t, $J=8\text{Hz}$ , $\text{CH}_2\text{Ar}$ ), 4.54 (1H, br.s., $-\text{OCHO}-$ ), 5.26 (2H, s, $\text{OCH}_2\text{Ar}$ ), 6.76 (1H, s, ArH), 8.22 (1H, dd, $J=1.5\text{Hz}$ , 8Hz, ArH), 8.76 (1H, d, $J=8\text{Hz}$ , ArH)
20	14 4-hydroxy-2-[11-(2-tetrahydropyranoyloxy) undecyl] quinoline-N-oxide	$\text{CDCl}_3$ , 2.43 (2H, t, $J=7\text{Hz}$ , $\text{CH}_2\text{Ar}$ ), 4.58 (1H, br.s., $-\text{OCHO}-$ ), 5.99 (1H, s, ArH), 7.17-8.32 (4H, m, ArH)
25	15 4-hydroxy-2-(10-carboxydecyl) quinoline-N-oxide	$\text{CDCl}_3 + \text{CD}_3\text{OD}$ , 2.30 (2H, t, $J=7.5\text{Hz}$ , $\text{CH}_2\text{CO}_2\text{H}$ ), 2.95 (2H, t, $J=8\text{Hz}$ , $\text{CH}_2\text{Ar}$ ), 6.36 (1H, s, ArH), 7.4-8.40 (4H, m, ArH)
30	16 4-hydroxy-2-(11-aminoundecyl) quinoline-N-oxide · hydrochloride	$\text{CDCl}_3 + \text{CD}_3\text{OD}$ , 2.99 (2H, t, $J=7.5\text{Hz}$ , $\text{CH}_2\text{NH}_2$ ), 3.25 (2H, t, $J=8\text{Hz}$ , $\text{CH}_2\text{Ar}$ ), 7.16 (1H, s, ArH), 7.77-8.60 (4H, m, ArH)

	Ex. No.	Compound	NMR δ (ppm)
5	17	4-hydroxy-2-[11-(N-benzylaminoundecyl)] quinoline-N-oxide	CDCl <sub>3</sub> , 2.50(2H, br.s, CH <sub>2</sub> NHCH <sub>2</sub> -Ar), 2.72(2H, dist. t, J=7.5Hz, ArCH <sub>2</sub> ), 3.93(2H, s, CH <sub>2</sub> NHAr), 5.88(1H, s, ArH), 7.99(1H, d, J=8Hz, ArH), 8.17(1H, d, J=8Hz, ArH)
10	18	4-hydroxy-2-[10-(N-hydroxyiminodecyl)] quinoline-N-oxide	CDCl <sub>3</sub> , 2.16(2H, q, J=5Hz, CH <sub>2</sub> CH=N-), 2.99(2H, t, J=6Hz, CH <sub>2</sub> Ar), 6.46(1H, s, ArH), 6.68(1H, t, J=5Hz, CH=N-), 7.35-8.40(4H, m, ArH)
15	19	4-hydroxy-2-(11,11-dimethoxyundecyl) quinolinē-N-oxide	CDCl <sub>3</sub> , 2.48(2H, t, J=8Hz, CH <sub>2</sub> Ar), 3.36(6H, s, OMe x 2), 4.42(1H, t, J=6Hz, CH(OMe) <sub>2</sub> ), 6.04(1H, s, ArH), 7.30-8.35(4H, m, ArH)
20	20	4-hydroxy-2-(10-formyldecyl) quinoline-N-oxide	CDCl <sub>3</sub> , 2.40(2H, t, J=8Hz, ArCH <sub>2</sub> ), 2.81(2H, br.s, CH <sub>2</sub> CHO), 6.40(1H, s, ArH), 8.10(1H, d, J=8Hz, ArH), 8.30(1H, d, J=8Hz, ArH), 9.77(1H, t, J=2Hz, CHO)

30

Example 21 Tablets

A 10% hydroxypropylcellulose solution is added to a mixture consisting of 100 g of 4-benzyloxy-2-(11-hydroxyundecyl) quinoline-N-oxide, 40 g of lactose, 18 g of corn starch and 10 g of carboxymethylcellulose calcium, and the mixture is kneaded. The mixture is then granulated

by an extrusion granulator with 1.0 mm basket, and the granules are dried at 60°C. The dried granules are screened on a 16-mesh sieve, and magnesium stearate is added to the screened granules to prepare tabletting  
5 granules. According to the ordinary procedure, tablets, 8 mm in size, each containing 100 mg of the N-oxide in one tablet (170 mg), are prepared.

Example 22      Capsules

10      A 10% hydroxypropylcellulose solution is added to a mixture consisting of 50 g of 4-benzyloxy-2-(10-carboxydecyl) quinoline-N-oxide, 80 g of lactose and 38 g of potato starch, and the mixture is kneaded. The mixture is granulated in the same manner as in Example 21, and  
15 after addition of magnesium stearate, capsules each containing 50 mg of the N-oxide in one capsule (170 mg) are prepared according to an ordinary procedure.

Example 23      Soft Capsules

20      At first, 10 g of 4-hydroxy-2-[11-(2-tetrahydro-pyranyloxy) undecyl] quinoline-N-oxide is dissolved in 100 g of soybean oil, and the solution is filled into capsules, each containing 10 mg of the N-oxide, according to the ordinary procedure, to prepare soft capsules.

25      Example 24      Ointment

At first, 20 g of 4-hydroxy-2-(11,11-dimethoxy-undecyl) quinoline-N-oxide is mixed with a mixture of white vaseline and liquid paraffin to prepare an ointment containing 100 mg/g of the N-oxide.  
30

Experimental Example

Inhibiting actions of test compounds shown in Table 2 on lipoxygenase in vitro were determined according to the following procedure.

5 Procedure for determining inhibiting actions on leukocyte 5-lipoxygenase:

Determination was conducted according to the modified B. A. Jakschik et al procedure [Biochim. Biophys. Res. Commun. 95, 103 (1980)]. That is, Leukemic basophilic

10 granulocyte (RBL-1, ATCC NO. CRL 1378) cells of rats were used as a 5-lipoxygenase enzyme source, and the cells and a test compound were contacted with each other in a 0.07 M tris hydrochloric acid buffer solution in the presence of 0.7 m moles of calcium chloride at 37°C for 5 minutes, and 15 then 20  $\mu$ moles of [ $^{14}$ C]-arachidonic acid was added thereto.

The mixture was subjected to reaction at 37°C for 5 minutes. The reaction product was extracted with ethyl acetate / methanol / 0.2 M citric acid (30 / 4 / 1) and the extract was subjected to a thin layer chromatographic

20 separation (developing solvent: petroleum ether / ethyl ether / acetic acid = 50 / 50 / 1), and the spot of 5-hydroxy-5,8,10,14-eicosatetraenoic acid in the product was scraped off and  $^{14}$ C was measured by a liquid scintillation counter.

The result is shown in Table 2, from which it 25 is obvious that the test compounds show an inhibiting action on the 5-lipoxygenase enzyme. The well-known compound BW-755C, i.e. 3-amino-1-(3-trifluoromethylphenyl)-2-pyrazoline hydrochloride is shown for comparison in Table 2.

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Table 2

	Compound Ex. No.	5-lipoxygenase- inhibiting concentration *1 IC50 ( μM )	Compound Ex. No.	5-lipoxygenase- inhibiting concentration *1 IC50 ( μM )
5	2	2.7 % *2	4	1.6 % *2
	13	11.5 % *2	3	0.28
	1 - (2)	7.7 % *2	14	0.16
	6	20.0 % *2	20	1.7
	7	33.1 % *2	15	2.7
	8	27.3 % *2	16	0.25
	9	27.0 % *2	17	0.27
	10	32.4 % *2	18	0.46
	11	36.6 % *2	19	0.18
	12	37.2 % *2	5	0.22
				BW-755C      4.0

\*1 Concentration of compound required for 50% inhibition of the enzyme activity.

\*2 Percent inhibition at 1 μM compound concentration.

25

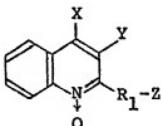
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WHAT IS CLAIMED IS:

1. A quinoline-N-oxide derivative represented by  
the formula:

5



10

wherein X is hydroxy, lower alkoxy, lower alkylthio,  
unsubstituted or substituted aralkyloxy, or unsub-  
stituted or substituted aralkylthio; Y is a hydrogen  
atom or halogen atom; R<sub>1</sub> is alkylene or alkenylene  
having 3 to 15 carbon atoms; Z is hydroxymethyl,  
lower alkoxy methyl, unsubstituted or substituted  
aryloxy methyl, tetrahydropyranoxymethyl, tetra-  
hydrofuranyloxymethyl; unsubstituted or substituted  
arylsulfonyloxymethyl, lower alkylthiomethyl, unsub-  
stituted or substituted arylthiomethyl, lower alkyl-  
sulfinylmethyl, unsubstituted or substituted aryl-  
sulfinylmethyl, lower alkylsulfonylmethyl, unsub-  
stituted or substituted arylsulfonylmethyl, amino-  
methyl, -CH<sub>2</sub>NHR<sub>2</sub>

15

20

25

wherein R<sub>2</sub> is lower alkyl, unsubstituted or  
substituted aralkyl, or unsubstituted or sub-  
stituted aryl,

-CH<sub>2</sub>NR<sub>3</sub>R<sub>4</sub>

30

wherein R<sub>3</sub> and R<sub>4</sub> are lower alkyl, unsubstituted  
or substituted aralkyl, or unsubstituted or sub-  
stituted aryl,

-CH<sub>2</sub>N<sup>+</sup>R<sub>5</sub>R<sub>6</sub>R<sub>7</sub>

35

wherein R<sub>5</sub>, R<sub>6</sub>, and R<sub>7</sub> are lower alkyl, unsub-  
stituted or substituted aralkyl, or unsubstituted  
or substituted aryl, where the counterion is an  
anion of acid or a hydroxyl ion,

-COR<sub>8</sub>

wherein R<sub>8</sub> is a hydrogen atom, lower alkyl or hydroxy

-CH(OR<sub>9</sub>)<sub>2</sub>

5 wherein R<sub>9</sub> is lower alkyl, iminomethyl, hydroxyiminomethyl, or a halogen atom, and its salts.

2. A quinoline-N-oxide derivative and its salts  
10 according to claim 1, wherein the substituent appearing in said substituted aralkyloxy, substituted aralkylthio, substituted aralkyl, substituted aryloxymethyl, substituted arylsulfonyloxyethyl, substituted arylthiomethyl, substituted arylsulfinylmethyl, substituted arylsulfonylmethyl and substituted aryl is a substituent on the aryl ring and  
15 is selected from the group consisting of lower alkyl, lower alkoxy, halogen atom, nitro and hydroxy.

3. A quinoline-N-oxide derivative and its salts  
20 according to claim 1, wherein R<sub>1</sub> is alkylene or alkenylene having 5 to 15 carbon atoms.

4. A quinoline-N-oxide derivative and its salts  
according to claim 1, wherein said salts are pharmacologically acceptable base addition salts or pharmacologically acceptable acid addition salts.  
25

5. A pharmaceutical composition, which comprises a quinoline-N-oxide derivative defined by claim 1 or a pharmacologically acceptable salt thereof, as an active ingredient, and at least one pharmaceutically acceptable carrier.  
30



EUROPEAN SEARCH REPORT

0177764  
Application number

EP 85 11 1243

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl.)
A	CHEMICAL ABSTRACTS, vol. 92, 1980, page 115, no. 191852m, Columbus, Ohio, US; P. RICCIO et al.: "Interaction of 3-(3H)-2-n-nonyl-4-hydroxyquinoline-N-oxide with submitochondrial particles from beef heart. I. Inhibition of respiratory activity", & BOLL. SOC. ITAL. BIOL. SPER. 1979, 55(23), 2506-11 * Abstract *	1,5	C 07 D 215/60 C 07 D 405/12 A 61 K 31/47
P, A	EP-A-0 128 374 (KYOWA HAKKO KOGYO) * Claim 1 *	1,5	
-----			
TECHNICAL FIELDS SEARCHED (Int. Cl.)			
C 07 D 215/00 C 07 D 405/00 A 61 K 31/00			
The present search report has been drawn up for all claims			
Place of search THE HAGUE	Date of completion of the search 09-12-1985	Examiner ALFARO I.	
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone	T : theory or principle underlying the invention		
Y : particularly relevant if combined with another document of the same category	E : earlier patent document, but published on, or after the filing date		
A : technological background	D : document cited in the application		
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P : intermediate document	& : member of the same patent family, corresponding document		